

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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*(First in an occasional series)***What Drives NIH Scientists?****A NEED TO KNOW
THE ORIGINS OF CANCER
SPARKS A CAREER PATH***by Myrna Zelaya-Quesada, NIAID*

Katherine Calvo remembers that “as a young girl I wanted to become either a scientist, a doctor, or a constitutional lawyer.”

Two out of three, as they say, isn't bad, especially when the two she has succeeded in becoming put Calvo at the cutting edge of research that is revolutionizing the diagnosis and treatment of cancer.

In a sense, motherhood almost derailed the pursuit of those aspirations and then, unexpectedly, it helped define them.

It was her son's illness that sparked her resolute journey through a rigorous MD/PhD program at the University of California, San Diego, and into an NCI residency, where for the past year, she has engaged in clinical pathology training while preparing for the research that for years she thought would remain a dream.

As a resident in the Laboratory of Pathology, Calvo will be using proteomics to map out the specific molecular pathways that are derailed in individual patients' tumors. She and her colleagues hope eventually to use cocktails of molecularly targeted inhibitors tailored for individual tumors.

“It is my dream that in the future

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Myrna Zelaya-Quesada

Katherine Calvo

From Art to Science**NIH HUMAN EMBRYO STEM CELL UNIT
SETS OUT TO CHARACTERIZE CELL LINES***by Celia Hooper and Fran Pollner*

At this stage, the mission of NIH's new Stem Cell Unit is a little like the cells it studies. For both pluripotent stem cells and the unit, life boils down to the basics—laying down foundations and definitions.

The unit, which grew its first human embryonic stem (ES) cell early last August, was established within NINDS, but with outward-looking and increasingly ambitious goals, which start with accurate definition of the characteristics of pluripotent human ES cells and how to grow them.

Within a year, the unit expects to produce a body of knowledge that will define and enhance the usefulness of most of the human ES cell lines that can be studied with federal funds.

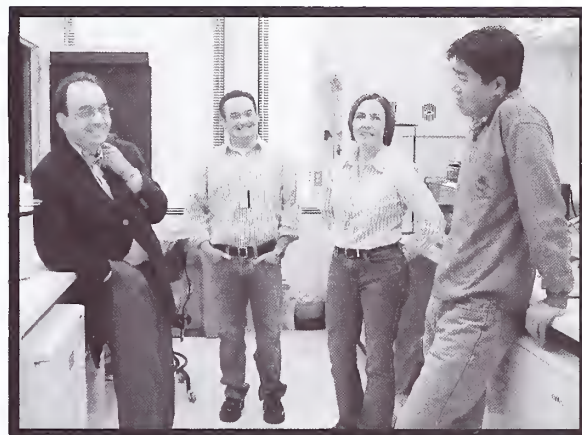
When *The NIH Catalyst* visited in early March, the unit consisted of four scientists, supervised by NINDS senior investigator Ron McKay, whose lab (molecular biology) had previously worked on mouse embryo stem cells and neuronal precursor cells. Key benchmarks in the unit's development thus far include:

■ Acquisition of 13 of the 17 currently approved human ES cell lines that are most readily available for federally supported research

■ Bringing six of the cell lines into active culture and beginning to define protocols for their growth (the others will be moved from freezer to culture within the year)

■ Rederivation of one colony from a single cell—that is, the cloning of a homogeneous stem cell population from a single cell

“If you are not able to clone a genetically homogeneous pure population



Fran Pollner

Stem Cell-Mates: (left to right) Ron McKay and three of the four NINDS scientists who are characterizing, comparing, and defining protocols for growing cell lines available in the NIH stem cell registry: Richard Pitts, Barbara Mallon, and Kye-Yoon Park

from a single source, you cannot do anything—no genetics, no biology,” McKay comments on the unit's latest accomplishment.

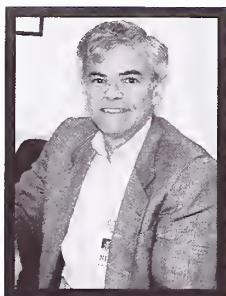
“Our being able to subclone the cells is a really important step forward. There are not very many people in the world who can casually say they can subclone human ES cells—and, actually, it wasn't

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THE 'I' IN NIH IS INNOVATION: EVOLVING INTRAMURAL RESPONSE TO AN IOM RECOMMENDATION



Michael Gottesman

Recommendation 8: Promote Innovation and Risk Taking in Intramural Research

The intramural research program should consist of research and training programs that complement and are distinguished from those in the extramural community and the private sector. The intramural program's special status obligates it to take risks and be innovative. Regular in-depth review of each component of the intramural program should occur to ensure continuing excellence. Allocation of resources to the intramural program should be closely tied to accomplishments and opportunities. Inter-institute and intramural-extramural collaborations should be supported and enhanced.

—“Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges”
Committee on the Organizational Structure of the National Institutes of Health
National Research Council, Institute of Medicine
July 29, 2003

In the last eight months, two blue ribbon panels were convened to look at the way we do research here at NIH. One was organized by the Institute of Medicine and the other by the NIH director, and both have issued recommendations that place a high premium on innovative, high-risk research (see *The NIH Catalyst*, September-October 2003, p. 13, and January-February 2004, p. 1).

Moreover, our now-famous internal “Roadmap” for NIH research similarly emphasizes ways to enhance the environment here for distinctive, high-risk research.

These deliberations, both internal and external, capture much of the spirit of NIH. After all, what drew many of us to NIH in the first place were the freedom and means to pursue tantalizing research paths that would be more difficult to travel under extramural funding mechanisms. Figuring out how to build on these strengths is, above all, rewarding work.

I thought I would use this column to present the evolving intramural response to the IOM recommendation (copied above)—and also to fire your enthusiasm to take your own research risks.

What We Have

The intramural program is designed to encourage long-term research investments in areas difficult to support elsewhere, while also providing an infrastructure for rapid research response to public health emergencies.

This is accomplished in four ways:

(1) NIH provides stable, relatively long-term support of creative senior investigators who were carefully chosen through national search processes either at the tenure-track or senior level.

(2) The rigorous and largely retrospective quadrennial review by external Boards of Scientific Counselors (BSCs) of all scientists with independent research resources encourages high-risk, innovative approaches to science.

(3) There are multiple mechanisms—such as bench-to-bedside awards—that encourage collaboration and teamwork within and across institutes.

(4) Our state-of-the-art laboratory and clinical research facilities help eliminate barriers to innovative science.

What We Are Building

The NIH director convened a Blue Ribbon Panel in 2003 to recommend steps to strengthen the NIH intramural clinical research program, especially with respect to the need to conduct distinctive, high-risk research and to complement extramural clinical research activities. This panel presented its recommendations to the Advisory Committee to the Director on

January 12, 2004, and they are currently being implemented.

Major changes in the clinical research program will include:

- A new NIH Clinical Research Oversight Board that will consolidate existing review mechanisms to allow more effective prospective planning and budgeting for clinical research across NIH

- A clinical research portfolio review group, composed of members of existing BSCs with clinical research expertise, to ensure that we can do clinical research that is distinctive and complements extramural research

- Improvements in NIH training and career development programs aimed at creating the next generation of innovative clinical researchers

- A new, senior-level position to help coordinate trans-NIH and intramural and extramural clinical research activities

BSC and SD Involvement

In targeted discussions with the NIH director and me, the BSC chairs agreed that out-of-the-box thinking is desirable. They were enthusiastic about piloting novel ways to encourage research support for especially innovative science. They agreed that scientists who pursue high-risk, potentially high-return research ought not be penalized by cuts in funding if projects are not successful.

A subsequent discussion with the scientific directors (SDs) reinforced the need for a better definition of what constitutes high-risk research and for the development of intramural pilot programs to encourage more of it. An SD subcommittee will develop specific definitions and recommendations.

A process has been established to facilitate trans-NIH programs of very high public-health and/or research importance. This includes naming lead institute(s), under the auspices of the Office of Intramural Research, for specific programs, as well as a governance structure and a mechanism for pooling resources and obtaining centrally available resources, such as space.

Examples already underway are the Porter Neuroscience Center (NINDS and NIMH, lead ICs), the obesity program (NIDDK, lead), the Behavioral Sciences Center (NHGRI, lead), and the NIH Stem Cell Unit (NINDS, lead; see story, p. 1).

As always, I welcome suggestions from you on additional ways to facilitate innovative science at NIH. And I invite you to drop a line to this publication (<catalyst@nih.gov>) about your own ongoing or anticipated forays into high-risk research.

—Michael Gottesman, DDIR

NEUROIMMUNOLOGY IN SHOCK AND TISSUE DAMAGE: IMPLICATIONS FOR BIODEFENSE TREATMENT STRATEGIES

text and photos
by Esther M. Sternberg M.D., Director
Integrative Neural Immune Program

Advances in neuroscience and immunology that underpin treatment strategies for shock and tissue damage can be quickly adapted to targeted biodefense strategies, investigators agreed at a workshop sponsored by the Integrative Neural Immune Program, NIMH, and NIAID. Other participants hailed from NINDS, NIAAA, NIA, NCI, NCCAM, and the extramural community.

Setting the stage for the business of the workshop, NIAID Director Anthony Fauci described the NIAID Biodefense Research Agenda and emphasized the nationwide infrastructure designed to translate basic research insights into targeted diagnostic, therapeutic, and vaccine strategies for biodefense^{1,2}.

Talking Points

Following are some of the salient issues discussed during the workshop.

■ NIAID's Charles Hackett addressed the rationale for targeting innate immune responses as a first line of defense against unknown pathogens and supported the focus on innate immune components for management of shock and tissue damage resulting from infection or toxins.

■ Reviewing the role of adenosine and adenosine receptors in shock and tissue damage, NIAID's Michail Sitkovsky highlighted the interplay between hypoxia and adenosine release in initiating and amplifying shock and tissue damage, as well as the protective effects of adenosine agonists.

■ Joel Linden, of the University of Virginia, Charlottesville, reported on his studies of adenosine agonists in the treatment of septic shock.

■ NIMH's Esther Sternberg reviewed neuroendocrine and neural pathways (hypothalamic-pituitary-adrenal axis, sympathetic and parasympathetic nervous system, and endocannabinoids) known to regulate both inflammation and cardiovascular tone in shock and tissue damage.

■ Cox Terhorst, of Harvard University, Boston, offered insights from his

studies of experimental colitis.

■ NIAID's Mahtab Moayeri presented observations from animal models of anthrax lethal toxin-induced shock.

■ Jane Welsh, of the University of Texas A&M, College Station, discussed the glucocorticoid responses in protecting against and exacerbating post-viral shock.

■ NIMH's Jeanette Webster elaborated on glucocorticoid receptor repression by anthrax lethal toxin.

■ NIAAA's George Kunos reported on endocannabinoid receptors in septic shock.

■ Kevin Tracey, of the North Shore-Long Island Jewish Research Institute, Manhasset, N.Y., explored the role of the vagus nerve and cholinergic agonists in the treatment of sepsis and shock.

Dualities

Several common themes emerged from these presentations and the subsequent panel discussion, moderated by NINDS' Audrey Penn and Richard Johnson, of Johns Hopkins University, Baltimore.

■ Much like overenhancement of adaptive immunity, overstimulation of innate immunity is a double-edged sword.

■ Similarly, mediators that regulate both inflammation and cardiovascular tone (hypotension) can either protect from or enhance shock and tissue damage.



NIAID Director Tony Fauci (top) and NIMH Director Tom Insel set the stage for the workshop

■ As an inducer of mediator release, hypoxia generates more hypoxia and tissue damage.

■ Neural and neuroendocrine factors deserve study both as potential molecular therapeutic targets and as factors contributing to individual variability in host susceptibility in the general population.

Directions

It was agreed that several agents already shown to be effective in treating shock and tissue damage in animal models exposed to known pathogens might well be quickly applied to treating shock and tissue damage from unknown biotoxins.

It was also agreed that fully effective management of patients exposed to biotoxins would include evaluation of responsiveness and activity of neural and neuroendocrine pathways that could contribute to individual variability related to age, sex, associated illness, concurrent medications, physical training, stress, nutritional deprivation, and other physiological stressors.

Investigators emphasized the importance of considering sex hormones and interactions between the hypothalamic-pituitary-gonadal axis and other neuroendocrine systems as variables that could modulate the effects of neural agents in the treatment of shock and tissue damage. ■

Biodefense Working Group and LISTSERV

The biodefense workshop served as a platform from which to launch a biodefense working group and interactive LISTSERV.

Coordinated by the Integrative Neural Immune Program, the group will share research findings, reagents, potential therapeutic agents, tissues, and access to relevant animal models.

A trans-NIH effort that brings together neuroscientists, immunologists, medicinal chemists, and others from multiple institutes, universities, and the FDA, the working group exemplifies the "multidisciplinary research team of the future" envisioned in the NIH director's research road map.

To join the group and the LISTSERV, contact Socorro Vigil-Scott at <VIGILSCS@intra.nimh.nih.gov>.

1. A.S. Fauci. "Biodefense on the research agenda. Commentary." *Nature* 421: 787 (2003).

2. NIAID Biodefense Research Agenda for CDC Category A Agents. Progress Report, Aug. 2003: <www.niaid.nih.gov/biodefense/research/strat_plan.htm>;

click onto title to download 41-page PDF file of the progress report.

WHAT DRIVES NIH SCIENTISTS:
KATHERINE CALVO

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the treatment of cancer will be as easy as taking antibiotics to cure an infection," Calvo says.

Beginnings

Calvo observes that she didn't exactly follow the paths of her two childhood idols—Madame Curie and Mother Theresa—when she opted to concentrate on international relations at Reed College (in Portland, Ore.) and then married and had two children.

It was through her husband, Ahmed, a physician and the CEO of a primary care IPA, as well as the president of the Alameda-Contra Costa AAFP (American Academy of Family Physicians) in California, that she was initially connected to the field of medicine.

"I was happy being a mom at home," she recalls, "but I still had a desire to be part of the world, to be an active participant." When her older child, Sean, was three, Calvo decided she wanted to practice medicine. She enrolled at Stanford University in Stanford, Calif., and "essentially started college all over again" in science to fulfill premed requirements.

Two years later, during a vacation to Disneyland, Sean became uncharacteristically lethargic and complained of pain when walking. His sister Leah, two years younger, showed no signs of fatigue. That evening, the Calvos noticed a bruise on Sean's shoulder. "I thought he might have gotten hurt while playing," but Ahmed insisted they see a pediatrician the next morning, Calvo recounts.

Although the pediatrician thought Sean had nothing more serious than a cold, Ahmed insisted that blood be drawn. The next day, while Calvo took a final exam on cancer in the oncology section of her human biology class, the pediatrician came to the Calvos' home and told Ahmed that a group of pediatric oncologists at the University of California at San Francisco were waiting to see Sean. Ahmed's suspicion that Sean had leukemia, which he had withheld from his wife, had been confirmed.

The Calvos were directed to the pediatric oncology ward at UCSF, where Sean was diagnosed with acute lymphoblastic leukemia with myeloid markers and a 1:19 chromosomal translocation.

Because Sean's prognosis was poor, the Calvos accepted their doctor's suggestion that Sean participate in a research study with an experimental che-

motherapy protocol. Consents and waivers signed, Sean was given the first dose of pills, liquids, and shots. IV infusions, spinal taps, injections, bone marrow aspirations, biopsies, and more blood tests would follow.

Hard Times

Over the next several months, five-year-old Sean pleaded not to be taken to chemo, and Calvo questioned whether she ought to pursue her career. She credits her son's physician with

ever: Some parents objected to Sean's presence for fear their children would soon have to deal with the death of a schoolmate, and a group of older children, third-graders, actually ganged up on Sean during one recess, removing his cap and laughing at his baldness.

Over time, education improved the understanding of parents and students, and the situation improved considerably; the lessons learned were indelible.

On the Road to Recovery And Discovery

In the ensuing three and a half years, Sean completed chemotherapy and regained his health and energy—and Calvo completed biochemistry and biology courses at Berkeley, applied to medical school, and was accepted into the UCSD MD/PhD program.

During her first year, she joined a lab at the Scripps Research Institute in La Jolla to delve into the mechanisms of programmed cell death. She also arranged to rotate through a leukemia lab.

"I decided I needed to know and do more," Calvo recalls. "The pressure of watching my son and other children suffer from cancer intensified my desire to go deeper into medicine and research. I wanted to understand what had happened to him on a molecular level."

She was captivated by the science of dissecting the oncogenic mechanisms of the transcription factors that induced the aberrant gene expressions that drove cells toward cancer.

Getting Down to Basics: Molecular Pathology

As a student in the Molecular Pathology Graduate Program, she worked simultaneously on several different projects: the structural biochemistry of E2a-Pbx1, homo- and heterodimerization properties, and the functional domains required for oncogenesis in a mouse marrow immortalization system; the cooperation of HoxA9 and Meis 1 in orchestrating blockage of cell differentiation and self-renewal in cytokine-specific contexts; and the mechanisms of oncogenesis by Nup98-HoxA9 in myeloid leukemia.

Her thesis work addressed the oncogenic mechanisms of homeobox genes that are targets of chromosomal translocation in leukemias.

After completing her PhD in molecular pathology, Calvo took the final two



Myrna Zelaya-Quesada

Katherine Calvo

"I wanted to find out what had happened to (my son) on a molecular level."

teaching her bedside manner and with urging her to continue her studies. She went to school in the morning three days a week while friends and family stayed with Sean. During his hospital stays, she slept on a cot next to his bed.

The first two months passed. Sean became so pale his skin was translucent; his hair fell in large patches; he spiked fevers and had bouts of neutropenia. His parents feared potentially fatal infections and monitored his neutrophil count. But they also wanted Sean to live as normal a life as possible and enrolled him in kindergarten at a Berkeley school reputed for its academic excellence and its progressive attitude.

Their experiences at the school fell a bit short of the school's reputation, how-

AT THE STARTING POINT

years of medical school and began applications for her residency. "My biggest dilemma at the time was whether I would go into pathology or hem/onc [hematology/oncology]," she says.

"And I wanted more than anything to visit the NIH (pathology residency program) . . . I never dreamed I'd be here."

"You Can Do that Here"

What she had wanted to do, she relates, was to be able to map the specific proliferative, differentiation, and apoptotic pathways that become altered in cells in the progression to a cancerous phenotype.

With the understanding that each type (and subtype) of cancer probably has a unique combination of altered proteins in key pathways, she reasoned that—using a combination of genomics and proteomics—early diagnosis could be based on identifying the specific altered pathways in each individual patient's tumor. The design of cocktails of specific molecular inhibitors to fight each individual cancer could then follow.

This was the sort of research she dreamed of pursuing, but she was not sure then that the dream was realistic. When she described her ideas to Lance Liotta, chief of the NCI Laboratory of Pathology and head of the pathology residency program, he looked at her and said simply, "You can do that here."

"I was blown away; I'm still blown away," she says, laughing.

At the Threshold

Sean has been in remission since 1993. Leah, now 15, moved from California to Bethesda when Calvo accepted her residency with NIH and attends high school in the area. Ahmed and Sean will move later this year when Sean graduates from high school. Ahmed is now busy recruiting his replacement as chief medical officer for the San Ysidro Health Center in San Diego—and Sean, who is drawn to bioengineering and medical school, is applying to colleges on the East Coast.

"My greatest hope," Calvo says, "is to make a difference in the lives of patients by advancing the fields of cancer diagnostics and treatment. We need more dedicated research to reach a point where cancers are diagnosed at the earliest stages and treated individually for the specific protein network of pathways that have gone awry." ■



Fran Pollner

On the Map: Dushanka Kleinman (at podium), NIDCR deputy director and assistant director for implementation of the NIH Roadmap for Medical Research, moderated a briefing that featured key organizers of the programs to reach the three main Roadmap objectives. Shown here are (l. to r.): NCCAM Director Stephen Straus, Amy Patterson, director of the NIH Office of Biotechnology Activities, and NIAMS Director Stephen Katz (**Re-engineering the Clinical Research Enterprise**); Ellie Ebreinfeld, chief of the NIAID Picornavirus Replication Section, and NIDCR Director Lawrence Tabak (**Research Teams of the Future**); and NIGMS Director Jeremy Berg and NIMH Director Thomas Insel (**New Pathways to Discovery**)

With the doubling of the NIH budget came a re-emphasis on NIH obligations to the public health, chief among them the need to translate laboratory discoveries into bedside therapies even more rapidly.

"But you can't translate a language you do not understand," Elias Zerhouni said, outlining the nine implementation routes mapped out to develop the tools and teams needed to grasp the emerging complexity of biological systems (see photo below).

The data generated in the last decade, Zerhouni said at a briefing for the NIH community, exceed the existing intellectual and physical tools to process them. That will change with implementation of the NIH Roadmap, an intricate and comprehensive plan for generating, understanding, and applying knowledge relevant to human health.

Hundreds of NIH investigators are already involved in particular Roadmap journeys—Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Imaging; Structural Biology

Bioinformatics and Computation Biology
Nanomedicine
High-risk Research
Interdisciplinary Research
Public-Private Partnerships
Re-engineering the Clinical Research Enterprise

—and the process is wide open for input from every interested party at NIH, said Dushanka Kleinman, in charge of Roadmap implementation. She said the two-hour session was intended "to give you just a little flavor of the incredible richness" of the project. She urged investigators to check out the Roadmap website for details—

<<http://nihroadmap.nih.gov>>

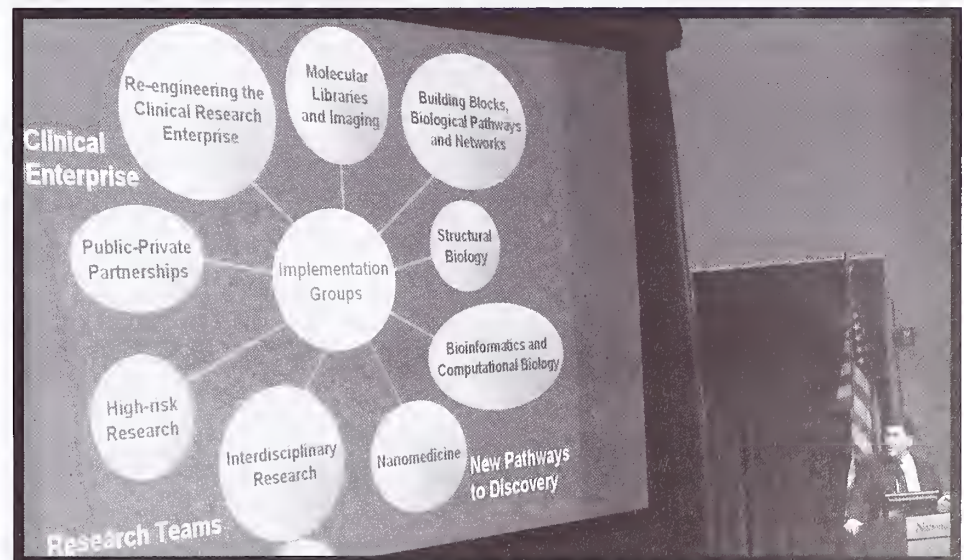
—and to sign on to the Roadmap LISTSERV.

Every IC, Kleinman said, has a Roadmap liaison, "or contact me directly, and I will match you up" with the group of particular interest, she suggested.

To view the briefing session, see

<<http://www.webconferences.com/nihroadmap/>>.

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NIH STEM CELL UNIT

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very obvious to us a month ago that we could do it."

Scientists around the world have been dazzled by the potential and realized properties of ES cells—including their ability to be propagated abundantly and indefinitely before being induced to differentiate into almost any cell type in the human repertoire. They hope to capitalize on these properties in the future, transplanting the cells into patients to replace diseased, damaged, and degenerating tissues otherwise beyond therapy.

A Matter of Definition: Cells and Protocols

But at this point, the unit's *raison d'être* is more mundane, albeit critical:

- To ensure that the cells are pathogen free
- To ensure they have normal karyotypes
- To define common properties of the cells
- To define standard operating procedures for growth

The unit hopes to turn what has been a notoriously difficult art into a reproducible science. "That's why this group exists," says McKay.

The unit's researchers, each of whom is responsible for growing a couple of the cell lines, note that the initial stocks of cells arrived with five different sets of instructions from five different suppliers—Wisconsin Alumni Research Foundation (WiCell Research Institute) in Madison, Wisc.; the University of California at San Francisco; BresaGen, Inc., in Athens, Ga.; MizMedi Hospital—Seoul National University in Korea; and Technion—Israel Institute of Technology in Haifa.

"This is a classic example of a little 'local culture.' Each of these groups has independently developed factors to grow their cells," McKay observes.

Their differences may be more perceived than real, the group agrees, and a goal of the unit is to test out each protocol, refining as they go, and see whether there may be a single common protocol that will work for all lines.

It also may be that differences in culture protocols are actually important for

the different cell lines, McKay says. Very slight differences in the timing of the initial derivation of the cells, or slight genetic differences between them, may lead to real differences in how the cells respond to different conditions. Over multiple passages or replating of cells, selection of certain cells—for example, those that grow more quickly—could also be driving a sort of evolutionary diversification of the cell lines or even selecting for cells more prone to oncogenesis.

By attempting to define a standard protocol and a standard cell—colonies from a single, cloned cell—the unit hopes to discern any real differences in nature vs. nurture for the cell lines.

The team will also experiment with ways to reduce culture variability attributable to feeder layers or other imperfectly defined components of the growth media.

"There's another cell in this whole game, and that's the mouse fibro-

blast," the feeder layer on which the human cells are grown. "We've talked to people who make human ES cells who say that if they fail it's because batches of mouse fibroblasts fail," McKay says.

The team will be prospecting for factors that optimize growth, including what they refer to as the "mystery factor" in mouse fibroblast cells. They will also experiment with growing cells without a feeder layer.

Establishing this bedrock foundation for defining cells and protocols is critical for human ES cell research, McKay says. "It's critical that you know where you started" for any subsequent experiments with the cells. The unit, he says, will provide access to a "common, normal cell."

He likens the importance of standardization of stem cells and their growth protocols to having standards for measurement of distance or purification of enzymes in the golden age of enzymology.

"If you don't know what cells you've got, you don't have a field."



Fran Pollner

The Inner Sanctum: laminar flow hood where the team cultures the human embryonic stem cells

Shifting Sands of Stem Cell Research

The Stem Cell Unit's attempt to lay this foundation comes at a time when human ES cell research is undergoing massive shifts. The day before *The Catalyst* visited the unit, the *New England Journal of Medicine* prepublished an article online that details the establishment of 17 new human ES cell lines by Harvard's Doug Melton and colleagues ("Derivation of Embryonic Stem-Cell Lines from Human Blastocysts"). Because the cells were extracted after the August 9, 2001, cutoff date for human ES cells that may be studied with federal funds, the Harvard group used private funds and facilities for their work—something that must also be done by any investigators seeking to use these new cell lines for their own stem cell research.

In an editorial accompanying the report, *NEJM* editors refer to the cell lines available in the NIH registry as "reportedly difficult to obtain, difficult to maintain, or poorly characterized," and they urge that Melton's cell lines become part of the NIH registry for NIH-funded researchers.

These problems underscore the urgency of the unit's mission, which will maximize the usefulness of the cell lines available for federal funding.

"Particularly now," McKay says, "when there's a very limited number of lines that can be used with NIH funds, there's an obligation on us to check them, to compare them, to determine their basic properties: Do they grow? Are they normal? We exist to ensure that human ES cells are grown in the right way and can be expanded in large numbers."

"And this group of people," McKay raves, pointing to his colleagues, "is the only group of people in the world who are doing this." By the end of the year, he says, 13 of the federally approved cell lines will be under study in the unit.

The Quest for Stability

Having a predictable standard cell will also be critical down the road. Researchers have begun to report that some of the federally approved stem cell lines are showing signs of chromosomal instability—for instance, picking up an extra chromosome after a large number of passages. McKay stresses that karyotypic instability would not be acceptable for therapeutic cells transplanted into patients.

Thomas Ried, NCI's chief of cancer genomics in the Center for Cancer Research, has collaborated with the unit to do spectral karyotyping on a half-dozen of the cell lines. So far, he says, "the majority showed a normal karyotype. Only one showed a gain of chromosome 17." Ried considers karyotyping a "very important and reasonable first step to test the genomic integrity of these cells."

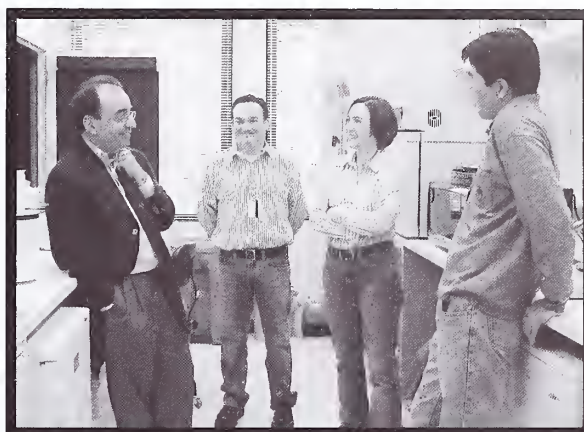
McKay says the intense focus on refining and defining the ES cell "is just the beginning." Beyond karyotyping, the unit will probe for more subtle genetic changes in the cells.

"We're looking at gene expression by antibody techniques and by PCR. We're interested in learning whether these cells express transcription factors we know to be involved in early differentiation . . . How you grow the cells will be linked, one assumes, to the levels of expression of these different genes.

"And we'll be able to tell people, 'if you grow this cell type *this* way, it will have the following properties—and when you put it through the FACS machine, you'll see *this* profile.'"

Vive la Différence

In the years ahead, the unit will move toward characterizing and standardizing procedures for differentiating the cells—applying growth factors to induce them to grow into potentially transplantable therapeutic cells. Thus far, and following closely McKay's research on mouse ES cells, the main efforts in differentiating the human cells have been steering them toward neuronal development, including production of dopamine-secreting neurons.



Fran Pollner

Ron McKay (left) extolls the efforts and caliber of his Stem Cell Unit team (present are Richard Pitts, Barbara Mallon, and Kye-Yoon Park)

Support to establish the NIH Stem Cell Unit came from the NIH director's discretionary fund; most of the NIH intramural programs contribute to its continuing support. The scope of the unit's budget and research is overseen by a steering committee comprised of leading intramural and extramural stem cell biologists.

Prospects also "look promising" in terms of endodermal differentiation, McKay says, noting that "we can make endoderm pretty efficiently" and that a cell of particular therapeutic interest—the pancreatic islet cell—arises from endoderm.

McKay's murine ES cell research also points to oligodendrocytes and multiple sclerosis as tempting future targets for differentiating ES cells. "The oligo precursor is easy to grow and easy to expand, and when we put these oligos back into the brain of a rat model of human disease, they made very nice myelin. So when you think of the first clinical uses of human ES cells—in, say, two to three years—you might think of oligodendrocytes and the multiple sclerosis program [at NINDS]. I talk with Roland Martin [at NINDS] about this."

McKay starts listing others on campus with whom he talks shop—among them Pam Robey (NIDCR, mesenchymal stem

cells), David Bodine (NHGRI, hematopoietic stem cells), Cindy Dunbar (NHLBI, clinical hematopoietic stem cell transplantation)—an emerging cell therapy network of basic and clinical investigators with an eye toward the future (see box, this page).

Perhaps more immediately than human therapy, McKay says, will be use of the ES cells for basic research to study the effects of gene manipulations on specific tissues and development that cannot currently be studied in vitro. This work is closely allied to gene therapy, which may also profit from careful ES cell groundwork. He again stresses the importance of having a genetically defined starting material

for such research. "Garbage in, garbage out," he says flatly.

With the Click of a Mouse

With standardization efforts over the next two to three years, McKay expects researchers will feel secure about the predictability of human ES cells.

The unit plans to help other NIH stem cell labs by publishing standard operating procedures and data characterizing the cells on its website:

<<http://stemcells.nih.gov/scientificResources/nihscunit.asp>>.

They will also share specific expertise on acquiring and growing the different cell lines with individual labs. Although growing large numbers of undifferentiated cells is very labor intensive, McKay says at least obtaining the knowledge of how to get and grow the cells should not be, if the unit does its job.

"We want to make it easy." ■

Stem Cell Users Group Looks to A Future for Clinical Stem Cell Research

In a parallel and complementary vein, efforts are under way to coordinate the efforts of NIHers pursuing all varieties of potential clinical applications of stem cell research.

In February, Betsy Nabel, NHLBI's director of clinical research programs, assembled scientists studying all types of stem cells—including hematopoietic, mesenchymal, and other multipotent cells from adults. An emphasis of the group will be on translational and clinical research.

Intramural investigators who would like to participate in this group to share ideas, expertise, reagents, or techniques should contact Sandy Moyer (<moyers@nhlbi.nih.gov>) to be added to the group's e-mail list.

Although human embryo stem cells are still far from ready for investigations in patients, protocols using adult stem cells

are already under way at NIH. The new users group hopes that efforts now to coordinate resources and teamwork for adult stem cell research will pave the way when embryo stem cell research is ready to go clinical.

The group has two working committees. The first, led by Elizabeth Read and Kathy Zoon, is reviewing resources and needs to identify potential gaps for the development of stem cell products for clinical use. The second, led by Cindy Dunbar and Ron McKay, is putting together an NIH-wide stem cell workshop, tentatively titled "Moving Stem Cells from the Lab to the Clinic: Where Do We Stand and What Needs To Be Done?" The workshop is planned for **May 24** in Masur Auditorium.

—ch

CTC CLARIFIES CRITERIA FOR TENURE AT NIH

by Arlyn Garcia-Perez, Ph.D.
Assistant Director, OIR,
Executive Secretary,
Central Tenure Committee

"To ensure a strong tenure system that provides the intramural research program with creative and productive scientists, an NIH-wide Tenure Committee, advisory to the Deputy Director for Intramural Research . . . should be established to review and recommend for approval (or rejection) all potential appointments to tenure."

—NIH IRP Report of the External Advisory Committee, Director's Advisory Committee, Nov. 17, 1994

On January 5, 2004, nearing the 10th anniversary of its inception, the NIH Central Tenure Committee (CTC) conducted its first-ever retreat for a look back and a future vision. Invitations to all past and present CTC members, scientific directors, and members of special panels advisory to the CTC were extended, and fully 70 percent gathered together enthusiastically for a meeting in Building 1, Wilson Hall. (See <<http://www1.od.nih.gov/oir/sourcebook/comm-adv/ctc.htm>> and <<http://www1.od.nih.gov/oir/sourcebook/comm-adv/ctc.htm#Mem>>.)

Michael Gottesman, deputy director for intramural research (DDIR) and CTC chair, presented summary data on the tenure rate at NIH since 1994 (<<http://www1.od.nih.gov/oir/sourcebook/irp-policy/tenure.htm>>).

For the cohorts of investigators who started on the tenure track in 1994 and 1995, 56 percent and 58 percent, respectively, achieved tenure. Since more than 20 percent of investigators who started in 1996 and subsequent years are still on the tenure track, the overall tenure rate for those cohorts is still changing.

Review by the CTC is the last step in the review process for tenure, and nearly all candidates who reach that point are indeed approved for tenure: 90 percent of all tenure-track investigators reviewed by the CTC since 1994 received tenure (in the same period, 91 percent of all outside candidates reviewed by the CTC for tenure also received it). Thus, nearly all individuals who do not achieve tenure from the tenure track fail to do so before they are reviewed by the CTC.

After questions on the data, the DDIR introduced an outline of criteria for tenure that the CTC has traditionally valued as fundamental. The ensuing thoughtful exchange and lively dialogue produced a draft that ultimately resulted in the consensus document printed on this page. ■

Criteria

■ High quality, originality, and impact of scientific contributions to a specific field and biomedical research more generally

- ◆ quality of studies, including scientific rationale and methodological rigor
- ◆ innovation and originality in the form of new ideas, approaches, discoveries and paradigms that open lines of further inquiry, including discovery and development of technological approaches, as well as design, development, and implementation of clinical trials and population studies
- ◆ scientific, clinical, and/or public health impact of published work
- ◆ upward trajectory expected following tenure

■ Independence

- ◆ independent research as evidenced by primary and senior authorship on original research publications
- ◆ for team research, clear evidence of distinct intellectual contribution to the research; members of research teams should demonstrate peer recognition of their specific contributions and some publications should highlight their distinctive research

■ Productivity relative to resources

- ◆ quality and quantity of publications (e.g., an original paper in a high-impact journal is considered more consequential than several papers in specialty, lower-impact journals)
- ◆ reputation of journals in which peer-reviewed papers are published, including specialty journals appropriate to the candidate's field
- ◆ patents and CRADAs
- ◆ timely deposition of data (in particular, large data sets) in freely available public databases; recognition given to high-quality data made avail-

able electronically to the research community, in some cases not directly linked to conventional journal publication(s)

■ National/international recognition and leadership

- ◆ peer recognition for developing an important body of work with a unifying theme, evidenced in letters of recommendation from the leaders in the field
- ◆ invited lectures and publications
- ◆ membership on editorial boards or as invited journal reviewer
- ◆ participation in grant review panels for NIH or other funding organizations
- ◆ ability to forge multidisciplinary partnerships, taking advantage of the breadth and depth of the NIH scientific and clinical environment
- ◆ honors and awards
- ◆ election to scientific societies
- ◆ IC programmatic need that evidences distinct and important contributions to the mission of NIH may be considered

■ Mentorship abilities and activities

- ◆ success in training and mentoring junior colleagues at all levels as evidenced by their professional progress, competitive funding, and/or publications

■ High ethical standards and integrity in directing and conducting research

■ NIH citizenship and collegiality

- ◆ IC or NIH-wide activity or committee participation (e.g., Scientific Interest Group, IRB, ACUC, WSAs, Faculties, etc.), clinical service, and other activities that promote the scientific enterprise at NIH and more broadly

Documentation to Assess Fulfillment of the Criteria

- Updated and accurate C.V. and bibliography, including all necessary information that addresses the criteria for tenure
- Letters of recommendation from the leaders in the field (at least six from noncollaborators)
- BSC reports, with particular emphasis on the most recent one (must be within the past two years for the Central Tenure Committee)
- Recommending memorandum from the Laboratory/Branch Chief or Scientific Director, through IC Director, specifically addressing the recommendation for tenure
- Report of the IC Promotion & Tenure Committee (only for tenure-track candidates)
- Report of the DDIR-approved Search Committee (only for outside candidates)
- The five publications that the candidate considers most important
- Description of future research plans by the candidate (no more than five pages)
- Detailed description of the resources (budget, personnel, space, other) available to the candidate from the beginning of the tenure track to date, with a timeline of changes during the tenure track (only for tenure-track candidates)

PEOPLE

RECENTLY TENURED

Tamas Balla received his M.D. from Semmelweis University School of Medicine, Budapest, Hungary, in 1979. He earned his Ph.D. from the Hungarian National Academy of Science in 1987. He did his postdoctoral training at NICHD between 1985 and 1987 and returned to NIH in 1989. He became a tenure-track investigator in 1997 in the NICHD Endocrinology and Reproduction Research Branch, where he is currently leading the Molecular Signal Transduction Section.

My engagement with research started when I was invited to join the laboratory of Andras Spat at the Department of Physiology, Semmelweis University, in Budapest as a second-year medical student. At the time, the group was investigating how the renin-angiotensin system regulates secretion of the adrenal mineralocorticoid hormone aldosterone in various forms of sodium deprivation. The importance of this question is underlined by the fact that many of the currently used antihypertensive drugs target the renin-angiotensin-aldosterone axis.

After finishing medical school, I joined the faculty in the physiology department and worked on the mechanism(s) by which the pressor peptide hormone angiotensin II (AngII) increases adrenal steroid secretion. More specifically, I tried to identify the molecular events initiated by the binding of the peptide to its cell-surface receptors.

At that time, little was known about the second messengers that mediate the effects of AngII in its target cells. However, the notion that increased phosphoinositide turnover is an early signaling event in the stimulatory actions of certain hormones and growth factors that elevate cytoplasmic Ca^{2+} concentration was beginning to emerge. In a series of studies, my colleagues and I established that AngII receptors used the phosphoinositide- Ca^{2+} signaling cascade in the adrenal, a result that was consistent with other labs' findings on AngII receptors in other tissues.

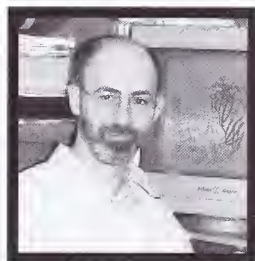
When I came to the NIH in 1985 as a postdoctoral fellow in Kevin Catt's group at the Endocrinology and Reproduction Research Branch of NICHD, I continued to explore the increasing complexity of inositol lipid and phosphate metabolism

and its connection to Ca^{2+} signaling, using the AngII receptors as a model system. Using HPLC to separate the various forms of inositol phosphates in metabolically labeled cells, we clarified the metabolic fate of the second messenger $Ins(1,4,5)P_3$, and we identified additional, highly phosphorylated inositol phosphates in the cells and described a novel pathway connecting them to $Ins(1,4,5)P_3$.

This period was the golden era of research on inositol phosphate- Ca^{2+} signaling. During this time, scientists described, isolated, and cloned the various forms of the phospholipase C enzymes, the GTP-binding proteins linking the receptors to phospholipase C activation, the protein kinase C isoforms that are activated by diacylglycerol, and the inositol 1,4,5-trisphosphate receptor calcium channels. The excitement and publicity surrounding this research topic was tremendously inspiring and has fueled my engagement in this rapidly expanding research field ever since.

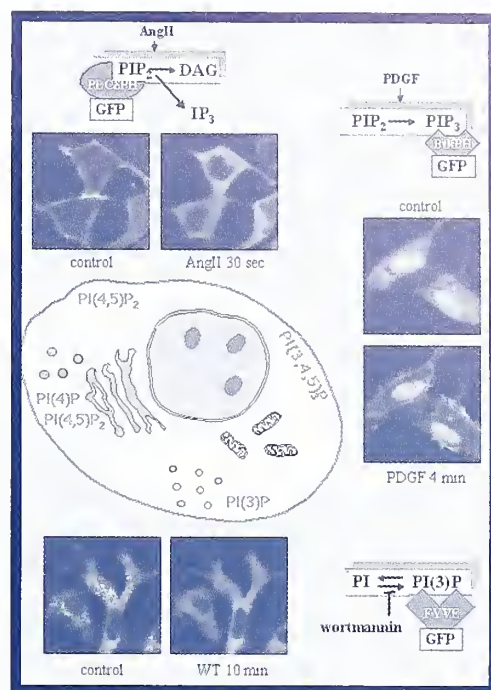
The current work of my research group was initiated by studies in the mid-1990s when we observed that the phosphoinositide precursors for receptor-mediated production of $Ins(1,4,5)P_3$ are synthesized by a phosphatidylinositol 4-kinase (PI4K) activity that is sensitive to PI 3-kinase inhibitors, such as wortmannin. This distinguished it from the other, membrane-bound PI4Ks known at the time. This led our lab to the isolation and molecular cloning of two soluble bovine PI4Ks.

While studying the functions and regulation of these enzymes, which are found in distinct cellular compartments, I explored new ways to examine localized production of inositol lipids and follow their dynamics in intact single cells. We created fusion proteins consisting of the green fluorescent protein and small protein modules known to confer specific inositol lipid interactions. By expressing these modules specific for particular inositol lipids, we were able to track production and localization of several lipids in intact cells (see figure). This technique, which was also developed and used in several other labs, has become a driving force in understanding the spatial and temporal aspects of inosi-



Fran Pollner

Tamas Balla



tor lipid signals.

Research of the last 10 years has shown that the versatility of inositide-based signaling is almost unparalleled in biology; only the GTP-binding proteins are similar in their ubiquitously important regulatory roles. Inositides are involved in:

- Mediating the metabolic, proliferative, and antiapoptotic effects of hormones
- Regulating the trafficking of molecules between various organelles
- Controlling exo- and endocytosis
- Regulating almost all ion channels and transporters

Inositides have also been implicated in nuclear signaling events. Because of their pleiotropic functions, inositide-regulated processes are often relevant to human diseases, such as diabetes, malignancy, and immunodeficiency. They are also targeted and used by pathogenic agents (bacteria, viruses, and toxins) to gain access to cells, to move around in them, or to be assembled and released from them.

Given such complexity, it's important to focus on certain areas. Our current research deals with the PI4Ks and their roles in trafficking of G-protein-coupled receptors and with the regulation of the phosphoinositide pools utilized to generate Ca^{2+} signals. Ongoing studies are aimed at identifying regulatory partners of PI4K enzymes in various cellular compartments. We also are improving and using imaging tools to understand the spatial organization of early signaling events initiated by hormones and neurotransmitters.

RECENTLY TENURED

Amir Gandjbakhche received his Ph.D. from the University of Paris Denis Diderot in 1989. He joined NIH as a postdoctoral fellow in 1990, entered the tenure track in 1999 in the Laboratory of Integrative and Medical Biophysics, NICHD, and is now a senior investigator and chief of the Section on Biomedical Stochastic Physics.

The objectives of the section are to devise theories, develop methodologies, and design instrumentation to study biological phenomena that have elements of randomness in both time and space.

Currently, the main focus of my section is to develop quantitative theories applicable to in vivo quantitative tissue optical spectroscopy and tomographic imaging of tissues. To achieve this goal, we are taking a multifaceted theoretical, computational, experimental, and clinical research approach to bring the methodology and associated technology from bench to bedside.

My key scientific challenge is to use the spectroscopic power of light for in vivo functional imaging of thick tissue and thereby relate metabolic activities at the molecular and cellular level to tissue function and metabolism.

This work requires analysis of different optical sources of contrast, such as absorption (for example, by hemoglobin or varying chromophore concentration) and/or scattering. We emphasize exogenous fluorescent labels as specific contrast agents.

Some current projects and collaborations we're conducting include:

I. Time-resolved tomography of thick tissue: application to quantitative spectroscopy of breast tumors and the use of specific fluorescent markers for identifying disease processes: This approach uses a transillumination method in which a very short pulse of laser light (of ~picosecond duration) impinges on the tissue. Because of the scattering properties of tissue, photons experience random walks, resulting in temporal dispersion of their time of arrival at the detector, which records light intensities at each time window. This is called time-of-flight (TOF) of photons.

Although direct imaging of abnormali-

ties with high resolution is not possible, this temporal discrimination of photon paths by quantitative spectroscopy allows theoretical constructs that separate the effects of scattering from absorption, in principle yielding optical coefficients that are spectroscopic signatures of abnormal tissue embedded in thick, normal tissue.



Fran Pollner

Amir Gandjbakhche

I have devised theoretical constructs, based on a random walk theory on a lattice that uses time-dependent contrast functions, to derive optical properties and the size of an abnormal target from TOF data. I have applied this method to quantify optical properties of breast tumors for three patients presenting with invasive ductal carcinoma. The

tumors showed increased absorption and scattering. From the absorption coefficients at different wavelengths, we were able to estimate blood oxygen saturation for the tumors and surrounding tissue.

We found that the tumors are hypoxic and their blood volume is increased by about a factor of two compared with surrounding tissue, indicating increased vascularization. I plan to use this technique for monitoring breast cancer patients undergoing chemotherapy and to study metabolic activity in the breast and correlate the results with treatment outcome.

II. 3-D reconstruction of localized fluorescence: The development of fluorescently labeled cell surface markers has opened the possibility of specific, quantitative, and noninvasive diagnosis of tissue changes, the ultimate goal being noninvasive optical biopsy.

Toward this end, I have derived an exact mathematical expression for signals emitted through an optically turbid medium by fluorescent masses. This expression incorporates the dependence of the signal on many parameters, including absorption and scattering coefficients at excitation and emission wavelengths, depth, and quantum yield.

We have begun to apply these findings in a series of animal experiments in which we study the immune response to the presence of squamous cell carcinoma in the tongues of BALB-c mice. We inject the mice with antibodies to CD3 or CD19 conjugated with fluores-

cent molecules.

I was able to show that my model of diffuse fluorescent photon migration can separate the effects of light diffusion at a given depth from the actual distributions of the fluorescent antibodies, thereby permitting us to measure noninvasively the degree and pattern of antibody binding—essentially permitting us to image the neoplastic cells and the associated pharmacokinetics.

In related work with ORS-DBEPS and NCI collaborators, I am heavily involved in applying these quantitative approaches in the use of new optical molecular contrast agents such as quantum dots. This method has been successfully tested in vivo to study vascularization deep in the thoracic cavities of mice. (See DDIR's Web Board, January 2004 <<http://www.nih.gov/ddir/back04/04.01.30/index.html>>.)

III. Monitoring blood circulation in Kaposi's sarcoma (KS): In collaboration with two NCI clinical protocols, we are evaluating the effectiveness of antiangiogenesis drug treatment of patients with KS.

New drugs targeting angiogenesis or blood flow have led to a need to monitor blood circulation noninvasively. I am investigating the use of three imaging modalities to quantify different parameters associated with blood circulation: 1) thermography, 2) laser Doppler imaging (LDI), which produces two-dimensional images of blood flow over a defined area at 690 nm and 780 nm, and 3) multispectral imaging, which produces two-dimensional reflectance images at six wavelengths (700–1,000 nm, in increments of 50 nm).

I am testing these techniques in an NCI-sponsored clinical trial of antiangiogenic drugs for KS, a highly vascularized tumor in which angiogenesis and capillary permeability can play key roles in disease development and progression. No standard noninvasive technique has yet emerged for the assessment of the effect of antiangiogenic therapy on blood flow to the tumors.

To test the potential applicability of the three noninvasive methods for assessing vascular changes associated with KS, we conduct thermographic, LDI, and multispectral imaging of KS lesions, comparing them with contralateral, lesion-free sites prior to antiangiogenesis chemotherapy and after treatment.

Six patients have now finished the first

phase of the treatment, and preliminary results show that lesions with higher temperature and blood flow in the lesion (compared with the contralateral side) are improved after treatment. Confirmation with conventional biopsy suggests that cooler lesions are not responding to the treatment.

Another area of research is devising polarimetric methods to study the destruction of collagen network after radiation treatment.

As demonstrated by this diverse array of collaborative projects, I would conclude that, for investigators who are interested in quantitative, functional, and noninvasive optical methods, this is a great time to collaborate with my section!

Sam Hwang received his Ph.D. in Biochemistry from the University of Basel (Switzerland) in 1989 and his M.D. from Harvard Medical School in 1991. Following internship at the Brigham and Women's Hospital in Boston, he trained in dermatology at the University of California, San Francisco. After residency, he was awarded a Howard Hughes Physician Fellowship in the laboratory of Steven Rosen (UCSF). In 1997, he became a tenure-track investigator in the Dermatology Branch of the CCR, NCI, where he is currently a senior investigator.

My laboratory is interested in the roles of chemokine receptors in the biology of normal immune cells and cancer cells. The chemokine receptors form a large family of G-protein-coupled membrane proteins with seven transmembrane-spanning domains. These proteins bind to chemotactic cytokines (chemokines) and are best known for regulating directional migration in response to inflammatory stimuli.

My initial work at NIH addressed the mechanisms by which antigen-presenting cells migrate out of skin under inflammatory conditions and move to secondary lymphoid organs via afferent lymphatic vessels. We found that a specific chemokine receptor, CCR7, and its ligand, CCL21, played critical roles in the directed migration of antigen-presenting dendritic cells from the skin to dermal lymphatic vessels and then to lymph nodes. This was due to the high expression of CCL21 by lymphatic endothelial

cells and nodal stromal cells.

Based on prior work in leukocytes demonstrating the important roles of chemokine receptors in organ-selective leukocyte trafficking, we hypothesized that specific expression of certain chemokine receptors may facilitate cancer metastasis. In support of this supposition, preliminary studies in our lab indicated that human melanoma cell lines expressed CCR7 as well as the receptors CXCR4 and CCR10.

Interestingly, others have shown that the ligand for each of these receptors is expressed at high levels at common sites of melanoma metastasis. For example, CXCR4 ligand (CXCL12) is found in the lung, and CCR10 ligand (CCL27) is constitutively expressed in the skin.

To determine the function of these receptors in cancer cells, we overexpressed them in B16 murine melanoma cells (where they are usually absent) and then assessed changes in the trafficking or survival pathways of the transfected cells. Compared with control cells, B16 cells overexpressing CCR7 (CCR7-B16 cells) metastasized readily to the skin-draining lymph node after cutaneous implantation. In contrast, compared with control cells, CXCR4-B16 cells showed 6- to 10-fold increases in pulmonary metastasis and adhered far more efficiently to pulmonary endothelial cells in vitro.



Fran Pollner

Sam Hwang

To make these findings, we took advantage of our experience with an advanced in vitro imaging system that allowed us to observe and quantify real-time interactions of tumor cells with endothelial cells under shear stress conditions. This system allowed more realistic modeling of the interactions of tumor cells with vascular endothelial cells that occur in complex vascular spaces in vivo.

Skin is a common site for the metastasis of melanoma. We suspected that CCR10 played a role in skin metastasis because keratinocytes in skin constitutively produce the CCR10 ligand, CCL27. In vivo, CCR10-B16 cells formed progressive tumors in the skin, whereas control tumor cells could not. Skin-derived CCL27 contributed to tumor formation of CCR10-B16 cells, because neutralizing anti-CCL27 antibodies completely blocked tumor formation in the cutaneous environment.

In these experiments, we also determined that CCR10 activation led to striking resistance of tumor cells to apoptosis mediated by Fas-ligation and by exposure to cytotoxic CD8 T cells that target cells bearing melanocyte antigens. The resistance to cell killing was likely due to an observed increase in the activation of Akt (a known antiapoptotic signaling molecule) in B16 cells after CCR10 activation.

Taken together, our results suggest that chemokine receptors may effectively help cancer cells evade important immune cell killing mechanisms.

Our search for mechanisms by which immune cells move into and out of the skin has resulted in a new set of questions pertaining to the molecular basis for organ-selective metastasis. We have discovered that normal and malignant cells, to a striking degree, share certain trafficking mechanisms.

The most clinically promising result from this work is our demonstration that chemokine receptor activation can render cancer cells more resistant to apoptotic signals.

Indeed, my laboratory is now seeking to prove a corollary of that result, namely, that chemokine receptor inhibitors will increase the efficacy of conventional apoptosis-inducing therapies, such as chemotherapy or radiation in clinical treatment of cancer patients. ■

NCCAM Lecture

The NCCAM series of Distinguished Lectures in the Science of Complementary and Alternative Medicine continues Wednesday, **March 31**, with Bruce McEwen, professor and head of the neuroendocrinology lab at New York's Rockefeller University.

The lecture—"From Molecules to Mind: Stress, Individual Differences, and the Social Environment"—will be held from 12:00 to 1:00 p.m. in Masur Auditorium, Building 10. It may be viewed on the web at

<<http://videocast.nih.gov>>.

For more information visit

<<http://nccam.nih.gov>>

or contact Kate Haessler at (301) 348-1662 or

<nccamlecture@mathewsgroup.com>.

This event is free and open to the public. ■

Cancer Prevention Research

ASSESSING THE MOUSE AS A MODEL: NOT FLAWLESS, BUT QUITE ATTRACTIVE

The strengths and limitations of the mouse as a model for cancer prevention research dominated discussions at a retreat last fall held by the NCI Cancer Prevention Faculty.

Molecular biologists, mouse geneticists, epidemiologists, and clinical oncologists from diverse laboratories and branches took a step back and contemplated the work of the last two decades in preclinical in vivo models. Have they been useful in modeling human disease and in intervening in the process of cancer progression?

The faculty opened the retreat by agreeing to a broader definition of the scope of cancer prevention activities—not just preventing the disease but also delaying progression at any stage, thereby resulting in delayed cancer mortality (or mortality from other causes). They then assessed the track record of the mouse model within this context.

Mouse Cons and Pros

Specific limitations to the applicability of research in inbred rodents to a diverse human population include:

- Different metastatic patterns—common human cancers often metastasize to bone, lung, brain, and liver, whereas metastases are found predominantly in lung in mice.

- Some pathways of cancer in rodents, such as P450-mediated xenobiotic metabolism, are different in humans.

On the other hand:

- Genetically engineered mice susceptible or resistant to cancer have proved to be relevant models for testing hypotheses generated by epidemiological, laboratory, and treatment-based observations and in staging interventions in human disease.

- Mouse and human gene expression profiling is revealing that mouse models can be predictive for scoring tumor progression or regression in humans.

- New technologies—such as gene expression arrays and proteomics analysis, along with comparative genomic hybridization and fluorescence imaging—are accelerating the pace of discovery of new molecular targets and of early and intermediate cancer endpoints to be used in scoring outcomes of interventions.

These technologies, together with conditional mouse models engineered for susceptibility or resistance and the

Molecular Targets pipeline for drug development, are among the resources NCI offers interested investigators.

Some Mouse Studies

Nutrition. Points made on the role of nutrition in cancer included:

- Reduction of energy consumption by 20 percent in a mouse model was found to have an anticancer effect.

- The APC 1638 mouse model of intestinal cancer recapitulates the human situation of 60 years ago when the majority of tumors were located in the small intestine; that the administration of a “Western diet” to APC mutant mice shifts the cancer incidence to the colon suggests that changes in the American diet are contributing to this common cancer.

Combinations. Combinations of interventions, each targeting a different pathway, present an attractive possibility for circumventing the development of drug-resistant cancer cells. Current colon cancer prevention trials are targeting cyclooxygenase-2 and ornithine decarboxylase. Investigators emphasized the importance of context and its influence on whether a given combination of drugs is synergistic or antagonistic.

A Possible Extrapolation

It was noted that studies of cancer incidence ought to be undertaken in patients being treated for other diseases with potentially carcinogenic agents—for example, patients with type 2 diabetes being treated with PPAR- γ agonists, which have been implicated in cancer in animal models.

A future forum will focus on human cancers directly and formulate recommendations for molecular-targeted approaches to carcinogenesis prevention.

—Cancer Prevention Faculty steering committee members

To Keep in Touch

The Cancer Prevention Faculty (CPF) provides a forum for enabling and enhancing collaborations, interdisciplinary and multidisciplinary research, and translational science. For information on CPF activities, contact Nancy Colburn (<colburn@ncifcrf.gov>) or check the Sixty Second Update <http://ccr.cancer.gov/news/60second_update/>, a monthly e-mail sent to CCR staff containing announcements, awards, event schedules, and policy changes. ■

GPP Symposium

The first annual NIH Graduate Student Research Symposium will be held in Masur Auditorium on **April 23, 2004**, from 8:45 a.m. (registration, breakfast) to 5.

NIH Director Elias Zerhouni will open the conference, and Harold Varmus, former NIH director, will be among the featured speakers.

Graduate students from more than 50 universities who are completing their doctoral research in NIH laboratories through the Graduate Partnerships Program —

<<http://gpp.nih.gov/>>

—will present their research in talks and poster sessions. An “outstanding mentor” will be honored. ■



Harold Varmus, NIH director from 1993–1999, Nobel laureate, and president and CEO of Memorial Sloan Kettering Cancer Center in New York, returns to campus April 23 to speak at the first annual Graduate Student Research Symposium

Readers Needed

Recording for the Blind and Dyslexic (RFB&D) needs science readers!

RFB&D provides recorded textbooks for blind and dyslexic students and currently has a much greater demand for college and postgraduate level science texts than it can fulfill. Its most critical need is for specialists—chemists, physicists, doctors, computer scientists, and mathematicians—who can volunteer at the recording space at NIH. The group asks for a one hour/week commitment for at least six months. Training is provided.

Contact Sarah Scully at (202) 244-8990, or e-mail:

<sscully@rfbfd.org>.

Postdoc Gatherings

How to make life better for postdocs will be the sole concern of a daylong (8–5) meeting **April 15** at the National Academies of Science in Washington. For agenda and to register, see <http://www7.nationalacademies.org/postdoc/April_Agenda.html>.

Next, on **April 16 and 17**, the National Postdoctoral Association annual meeting will be held at the AAAS Conference Center in Washington. See <http://www.nationalpostdoc.org/annual_meeting/>.

FARE Alert

Attention NIH fellows: From **April 1–30, 2004**, you can apply for FARE 2005 travel awards. See

<<http://felcom.nih.gov/FARE>>.

CLINICAL RESEARCH TRAINING AT NIH: THE LONG (DISTANCE) AND SHORT OF IT

Long-distance learning for medical professionals has been made a lot easier, thanks to the NIH Clinical Center (CC) Office of Clinical Research Training and Medical Education. Established in May 2003, the office currently directs five distance-learning courses. Here's the line-up:

■ **Introduction to the Principles and Practice of Clinical Research** (<<http://www.cc.nih.gov/introclinres>>). Begun in 1995 with 25 students, the course attracted more than 650 health-care professionals in the 2003-2004 academic year, including students participating from as far away as Lima, Peru. To date, 3,417 health professionals have availed themselves of this program, which teaches medical researchers how to design and conduct a successful clinical trial.

In addition to the U.S. Naval Medical Research Center Detachment in Lima, other off-site locations this year include Meharry Medical College in Nashville; Morehouse School of Medicine in Atlanta; Children's National Medical Center, George Washington University Medical Center in Washington, D.C.; the State University of New York Medical University in Syracuse; the University of Texas Southwestern Medical Center in Dallas; and the University of Puerto Rico in San Juan.

■ **Clinical Research Training** (<http://www.cc.nih.gov/cc/cr/>). All clinical principal investigators with a protocol approved through the CC are required to take the course and successfully complete a final examination.

■ **Principles of Clinical Pharmacology** (<<http://www.cc.nih.gov/cc/principles/>>). Established in 1998, this course provides an introductory review of pharmacokinetics, drug metabolism and transport, assessment of drug effects, drug therapy in special populations, and contemporary drug development. In addition to the NIH location in Bethesda, Md., five off-site locations participated in the 2003-2004 course: Georgetown University School of Medicine, Washington, D.C.; Indiana University School of Medicine, Indianapolis; NIA, Baltimore; Northwestern University Medical School, Chicago; and the David Geffen School of Medicine of the University of California, Los Angeles. The program has enrolled 1,574 students since its inception and runs from September through April,

one day a week, at the CC.

■ **NIH-Duke Training Program in Clinical Research** (<<http://tpr.mc.duke.edu>>). Designed primarily for clinical fellows and other health professionals who are training for careers in clinical research, this course teaches research design, statistical analysis, research ethics, and research management. It's taught at the CC via videoconference from Duke and also by adjunct faculty on campus. Thus far, 31 students have received a Master of Health Sciences in Clinical Research from Duke University.

■ **The University of Pittsburgh's Training in Clinical Research Program** (<www.pitt.edu/~tcrp>). Like the NIH-Duke program, this program offers advanced training in clinical research through videoconferenced courses at the CC. The University of

*by Cherry Graziosi, program assistant,
and Frederick Ognibene, director,
Office of Clinical Research Training
and Medical Education, CC*

Pittsburgh confers either a Master of Science Degree upon completion of core curriculum courses plus 15 credits of elective courses. The university also offers a certificate to those who do not take the full course but complete an extensive summer program and seminars.

CC Director John Gallin observes that improving clinical research training is a major initiative of the NIH road map, introduced by NIH Director Elias Zerhouni last November.

"In the past," Gallin says, "researchers relied on mentors to teach them how to conduct clinical trials. We have established a formalized training program to fill this critical gap, and we're extending it worldwide."

For more information on any courses or programs offered by the Office of Clinical Research Training and Medical Education, call 301-496-9425. ■

Clinical Research Curriculum Certificate

The Office of Clinical Research Training and Medical Education also administers the **Clinical Research Curriculum Certificate** program.

Fellows and other allied health-care professionals who successfully complete the mandatory portion of the program receive a certificate.

An additional commendation is awarded with the completion of at least one of four supplemental or elective components.

The **mandatory components** of this certificate program are:

■ Enrollment in **Introduction to the Principles and Practice of Clinical Research** (<<http://www.cc.nih.gov/introclinres>>), including a final examination.

■ Successful participation in the course on **Ethical and Regulatory Aspects of Human Subjects Research** (videocast access at <<http://www.videocast.nih.gov>>)

■ Successful completion of on-line **Clinical Research Training** for all principal investigators; registration information is at

<<http://www.nihtraining.com/cc/crt>>;

content information is at

<<http://www.cc.nih.gov/cc/cr>>.

■ Successful completion of com-

puter-based training course for NIH IRB members

<<http://ohsr.od.nih.gov>> and either 1) IRB protocol approval as a principal investigator, or 2) a three-month "term" or attendance at at least four IRB meetings as an ad hoc member with responsibility for a protocol's review, or 3) if one cannot be a principal investigator on a protocol (IC variable), then serving as either a "protocol chairperson" (NCI model, for example) or "providing significant contribution to the writing of a protocol."

The **supplemental or elective components** are:

■ Successful completion of **Principles of Clinical Pharmacology** (<<http://www.cc.nih.gov/cc/principles/>>)

based on 75 percent attendance requirement

■ Successful completion of an FAES course in statistics or epidemiology

■ Completion of approved IC-based programs in clinical research

■ FDA experience (with, for instance, INDs, data monitoring, audits) through the annual **Reviewer Training: Introduction to the Regulatory Process** course offered by FDA/CBER. ■

A NOT-SO-BURIED TREASURE: THE NIH INTRAMURAL DATABASE

adapted from the February 17, 2004, NIH Record
by Rich McManus

If a historian were to chart the advance of NIH intramural science, there might be no better resource than the two yearly publications—now grown to a web site—once known as the Annual Reports and the Scientific Directory and Annual Bibliography (SDAB). Initially slim volumes of perhaps 100 pages, they had expanded to many hundreds before their launch into cyberspace in 1998 as the NIH Intramural Database (NIDB).

The NIDB is more robust than anything in print could be; it isn't limited by the constraint of deadline, nor is its size limited by the capacities of a bindery. It's managed in CIT's Division of Enterprise and Custom Applications, and it's owned by the Office of Intramural Research.

Like its paper predecessor, NIDB still includes annual bibliographies (all papers produced by intramural scientists each year), the scientific directory (of all scientific staff in the intramural programs), and the annual reports describing each principal investigator's activities, amounting to some 2,500 projects each year. But NIDB also includes an NIH "résumé," which provides NIH research and bibliographic information on all NIH researchers, not just principal and lead investigators.

"We see the NIDB as a key mechanism to enhance collaborations across ICs and to stimulate multidisciplinary research projects," says Joan Schwartz, OIR assistant director and NIDB business manager.

"For me, this is a dream come true," says Michael Gottesman, NIH's deputy director for intramural research. "It is an enormously valuable tool for accessing the richness of intramural research, not only for our own researchers but for the rest of the world."

For example, one can type "NIDDK PCR" in the "Searching NIH Annual Reports" page to find entries that include both NIDDK personnel and the polymerase chain reaction. Instantly, the first 10 of 13 identified reports surface, listed in order of relevancy. A click on any title discloses principal investigator, lab staff, total staff years dedicated to the project, keywords associated with the project, a summary of the work, and, lastly, publications generated by the research. Many of these citations contain a link to PubMed.

A newcomer to NIH can find his or

her intellectual home in moments tapping into the NIDB—one of the reasons CIT's Dale Graham, the site's technical manager, likes it so much.

"I used to be a researcher," said Graham, a computational biologist who earned a Ph.D. in molecular biology in 1970, taught and did research at Purdue University, at West Lafayette, Ind., and was a working scientist at NIH from 1980 to 1990. "There's lots of turnover in research staff at the NIH and by the time you leave, you're often just getting to know where the good stuff is"—some-

thing the "senior guys already know." NIDB, she says, is especially useful for younger workers just finding their niche.

First at NCI working on mammary tumor virus and then at NIDDK studying insulin-like growth factor, Graham was recruited by CIT to do the kind of scientific support work she's naturally been doing on the side. "I had already been spending lots of time helping fellow researchers with computers and with sequence analysis—I just loved it."

Her expertise in bibliographic software fueled her enthusiasm to convert

NIDB at a Glance

There are about 1,250 scientists (principal and lead investigators) working in NIH laboratories and clinics and another 3,000 researchers (fellows, postdocs, research assistants, etc.) supporting them. Each year, each scientist must produce one or more annual reports summarizing his or her research activities, including a bibliography of the publications resulting from that research.

In the past, this information was submitted on paper and, in the more recent past, in various electronic forms. The data were manually compiled and reformatted—a time-consuming, error-prone process—and then combined with the data from the Scientific Directory. This huge compendium was then distributed in hard copy within NIH and externally on request (for instance, to Congress).

But in 1998, Dale Graham and crew at CIT created a web-enabled database to streamline the collection, verification, and dissemination of all this NIH intramural research data—the NIH Intramural Database (NIDB). With the click of a mouse, it's accessible to everyone at NIH and—not to hoard this extremely valuable information—to everyone outside NIH as well. The NIDB search engine is located at

<http://intramural.nih.gov/search/>.

From this website, users can search through authors' names, key words, or combination of these. The search can also be restricted by IC and by year of publication. The NIDB provides a framework for uniform data collection, historical evaluation of the NIH intramural research program overall, and IC-specific assessment of ongoing programs and decisions for the future. It currently has the following components:

■ **Annual Reports.** Research reports, year by year, of projects maintained by principal and lead investigators. Includes data on approximately 2,500 research projects each year. Fully operational.

■ **Annual Bibliographies.** Publications resulting from the NIH intramural programs each year since 1999. Implemented in 2000. Data collection effort still not complete, especially for 1999 to 2001, and for NCI.

■ **Scientific Directory.** Lists of all intramural scientific staff members involved in research, classified by organization unit and leadership status, including their NIH intramural professional designations (IPDs). Much of this information is currently collected via the Annual Report, but a stand-alone module is in progress.

■ **NIH Mini-CV.** Summaries of all the information held by the NIDB on all NIH researchers, not just principal and lead investigators. It includes the three components above and items such as educational background. Individual researchers can log on and correct/add to the data indicated. Initially implemented in 2003; currently being revamped to improve speed and reliability.

For more information, contact Dale Graham, NIDB technical manager:

[<degraham@mail.nih.gov>](mailto:degraham@mail.nih.gov).

the august bound volumes of the old Annual Reports and SDAB into the new NIDB. The site today is run by a staff of three, with input from hundreds of intramural scientists.

Graham concedes that NIDB does require some effort on the part of intramural scientists, but she maintains the effort is well worth it—"it lets the world know what we're working on."

"It seems like gold to me," she says. "It provides a good assessment tool for recruiting; it lets like-minded scientists create their own networks. Anyone can tap into it to see who is working on problems that interest them."

Graham emphasizes an advantage NIDB holds over its paper predecessor—you can ask questions of it. "There are lots of different ways to mine these data," she says. "It's a good tool for assessing collaborative efforts, or for tracing the progress of a given project over a number of years. The PubMed links included in the bibliographies often lead to full-text articles."

NIDB also allows multiple institutes to share credit for research publications; the paper version only permitted one institute to stake a claim.

It takes a substantial amount of behind-the-scenes geek-work, she divulges, to keep the site working properly. But that has paid off in the site's



Tom Reichert

She's Got Them Eating Out of Her Hands: Dale Graham is perhaps uniquely qualified to milk data from somewhat recalcitrant donors—she has for the past 20 years been a llama rancher. Llamas, she notes, "are very intelligent, but not very affectionate"—appearances of affection from Tiercel (left) and Austin City Lights notwithstanding. Graham and her husband (who took the picture) keep 23 llamas on a 20-acre farm 70 miles southwest of Bethesda in Culpeper County, Va., where they have recently finished building their dream house—a log cabin.

"A llama," Graham observes, "is like a 300-pound vegetarian cat. Basically, the way they think is, 'If it's their idea, it's good. If it's your idea, it's bad.'"

Such insight equips Graham—who has seen llamas successfully trained to caddy on golf courses and been fascinated for decades with llama "thinking"—to run the NIDB ranch quite nicely.

recognition as a funded NIH "enterprise project" and in the growing numbers of daily hits, now ranging from 300 to 800. ■

To see for yourself just how incredibly useful the NIDB site is, visit
<<http://intramural.nih.gov/search/>>.

THE VIRTUAL CAREER CENTER: ONE-STOP JOB SHOPPING

Short of giving you your first pay check, the newly launched Virtual Career Center—

<<http://www.training.nih.gov/careers/careercenter/index.html>>

—offers just about everything a science-minded soul searching for a job or a route to one could ask for.

Developed by the Office of Education (OE) and designed to meet the needs of the NIH community and other students and professionals in science and medicine, the Virtual Career Center opens four portals:

■ Exploring Career Options, which provides self-assessment inventories, career pathways, and some instruction in such skills as grant writing and publishing articles

■ Continuing Your Education, which presents information on ad-

missions, application services, financial aid, loan repayment, grants, fellowships, survival skills, and medical schools and other professional programs

■ Employment Options and Opportunities, which plumbs the openings in industry, academia, and government

■ The Job Search Process, which offers tips on applying, interviewing, and negotiating for a position

All told, the Virtual Career Center contains 55 pages and 1,088 links—and is infinitely expandable.

"The range of career options open to young scientists is broad and continually evolving," says Brenda Hanning, acting OE director. "Many of the jobs students will have in the future may not have been invented yet. Our site will work to keep pace with new avenues of opportunity."

"The massive amounts of informa-

tion about medical and science careers can be overwhelming to anyone—novice or expert," observes Michael Gottesman, deputy director for intramural research. "What makes the Virtual Career Center such a valuable resource is that we have the most up-to-date information available on one web site."

Among sources of information reviewed for inclusion in the Virtual Career Center were articles and postings from leading science magazines and journals, specialty associations, and government agencies.

OE also enlisted the expertise of Margaret Dikel, a librarian who has been studying the Internet as a tool in employment and career exploration since 1993. For additional information on career development, see

<www.rileyguide.com>.

CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov; fax: 402-4303; or mail: Building 2, Room 2W23.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Chemical Genomics
- ... and Other Road-map Deliveries
- Outpatient Transplant Protocol

GETTING INTO NIH

Once the construction of the fence surrounding the NIH Bethesda campus is complete and the entrances fully operational, there will be a total of eight vehicle/pedestrian access gates and nine stand-alone pedestrian access gates.

All vehicle access gates will have a security guard, with pedestrian access available during business hours. The other nine pedestrian gates will be accessed electronically. Equipped with an electronic security system, expected to be in place before the summer, the pedestrian portals will allow NIH employees entry "just by waving their NIH ID badge in front of a card reader," says Arturo Giron, associate director for security and emergency response.

For added security, the pedestrian-only portals actually require two successive ID checks—first in front of the gate and then in front of an entryway to the campus.

For more information on the perimeter fence and its access gates, contact David Chung, Physical Security Management, at 301-496-6893.



VEHICLE AND PEDESTRIAN ENTRANCES

On Old Georgetown Road:

South Drive
Lincoln Drive (vehicle exit only)
Center Drive

On Cedar Lane:

West Drive
(Patient/Patient Visitor vehicles only.
Open to employees for pedestrian access)

On Rockville Pike:

North Drive
Wilson Drive
South Drive
Center Drive

PEDESTRIAN-ONLY ENTRANCES

On Cedar Lane:

West Drive
Garden Drive

On Old Georgetown Road:

South Drive
Northeast corner between Center Drive
and Cedar Lane
Lincoln Drive (just south of)

South End of Campus:

Near Building 14 Trailers
Between 41 lots and MLP-7

Rockville Pike:

Two entrances, one on each side of the
planned Visitor's Center near the
South Drive entrance (Metro)

The *NIH Catalyst* is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: catalyst@nih.gov

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